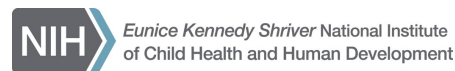


Infertility: An Increasing Problem Prompting Remarkable Advances

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Today's Talk

- Infertility – population perspective
 - Incidence & prevalence
 - Terminology & risk factors
 - Relevancy for health & disease across the lifespan
- Infertility – clinical perspective
 - Clinical evaluation & diagnosis
 - Medical advances in treatment

Changing Fecundity Landscape

- Earlier pubertal onset & progression (Buck Louis et al. 2008)
- Global declines in semen quality (Carlsen et al. 2004; Swan et al. 2003)
- Increasing interval for female reproductive age
 - 36.1 years for women born 1915-1919 versus 37.7 years for women born 1935-1939 (Nichols et al. 2006)
 - Earlier age at menarche (Herman-Giddens et al. 1997, 2001)
 - Slightly increasing age at menopause 51.4 years (Menopause Society, 2002)

Morning Spit-take





Being overweight may affect men's semen
quality

BY KATHRYN DOYLE

NEW YORK TIMES Dec 19, 2013

MIDDLE EAST: BUSH'S BIG GAMBLE



TIME



Babies vs. Career

WHICH SHOULD COME FIRST
FOR **WOMEN** WHO WANT BOTH?
The harsh facts about **FERTILITY**



www.time.com AOL Keyword: TIME



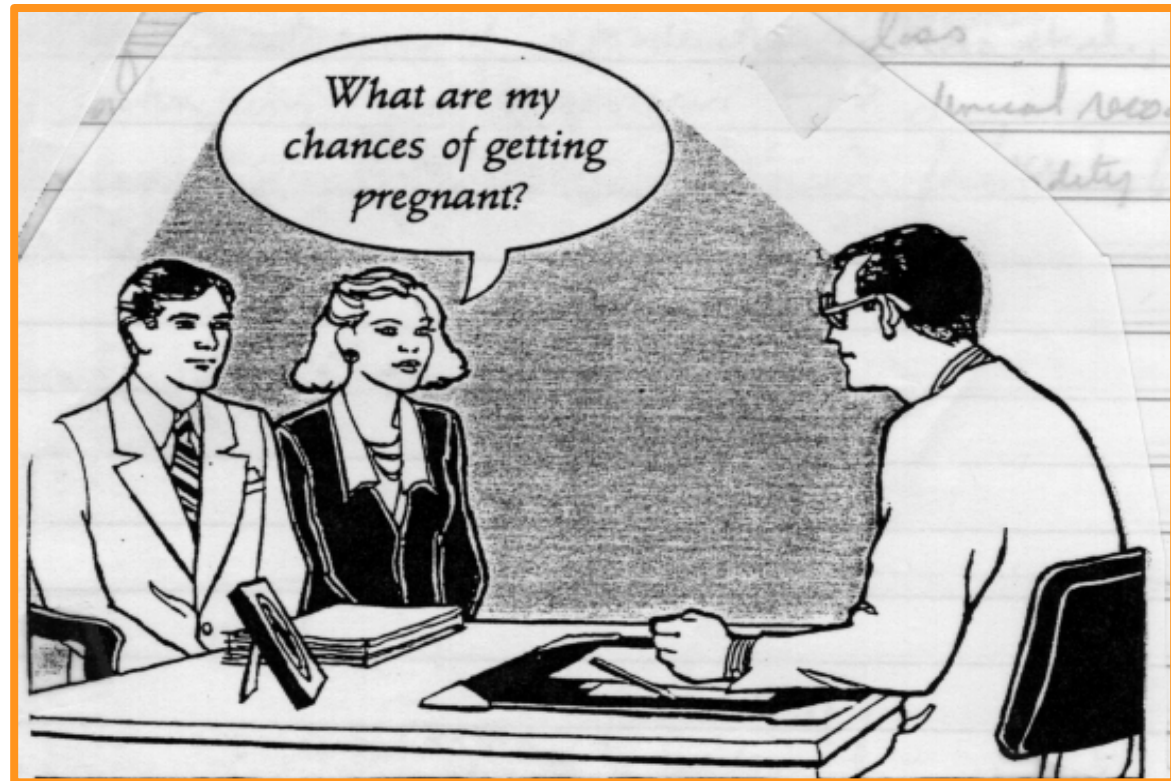
Who will have male factor infertility?

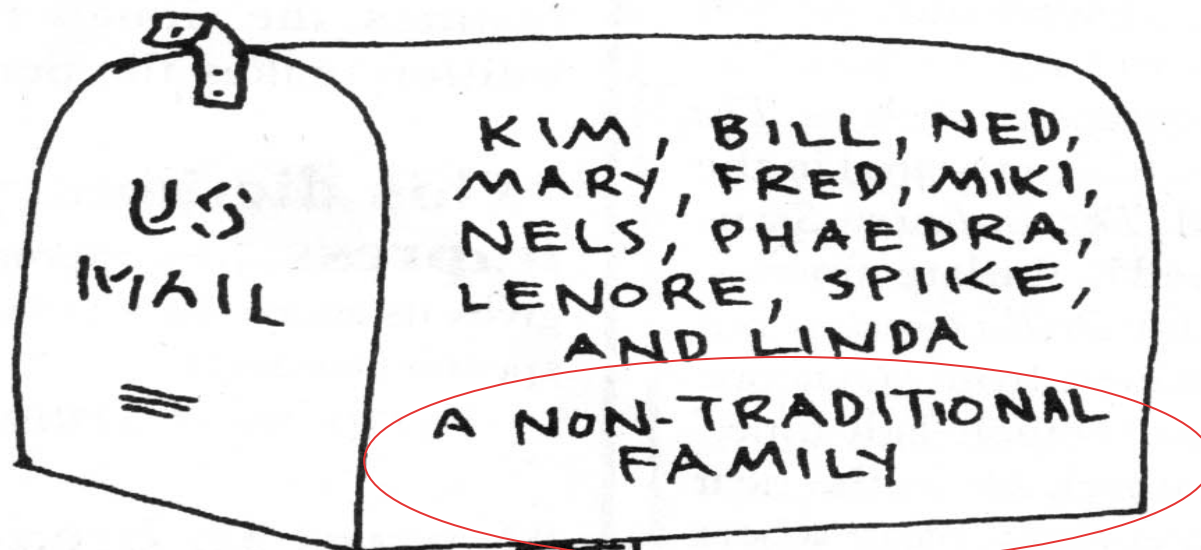


Who will have female factor infertility?

What are their chances of conceiving in the 1st month of trying? By 6 or 12 months?

- 100%
- 80%
- 60%
- 40%
- 20%
- 0%





KIM, BILL, NED,
MARY, FRED, MIKI,
NELS, PHAEDRA,
LENORE, SPIKE,
AND LINDA

A NON-TRADITIONAL
FAMILY

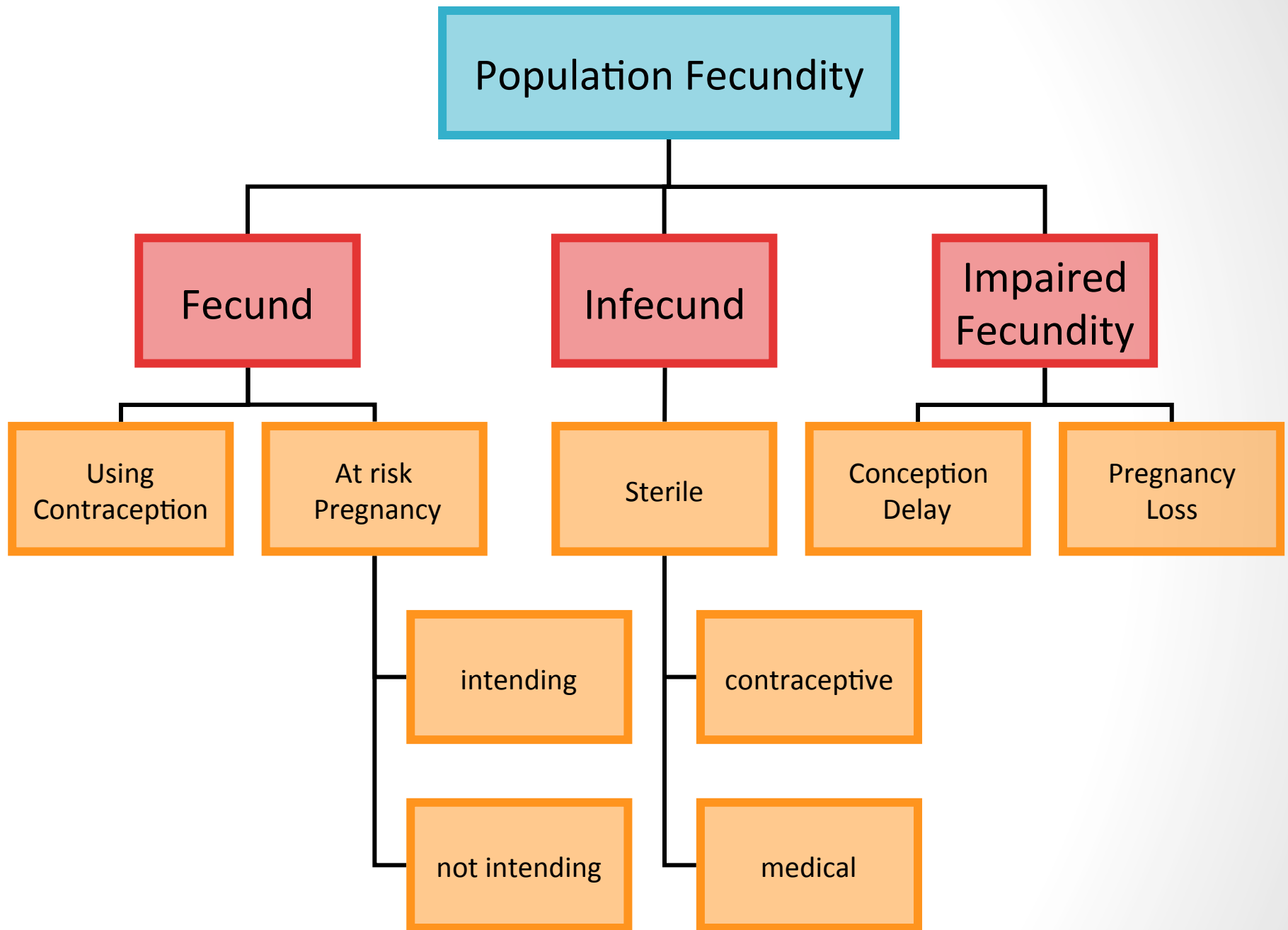
Terminology & Definitions

- **Fecundity**

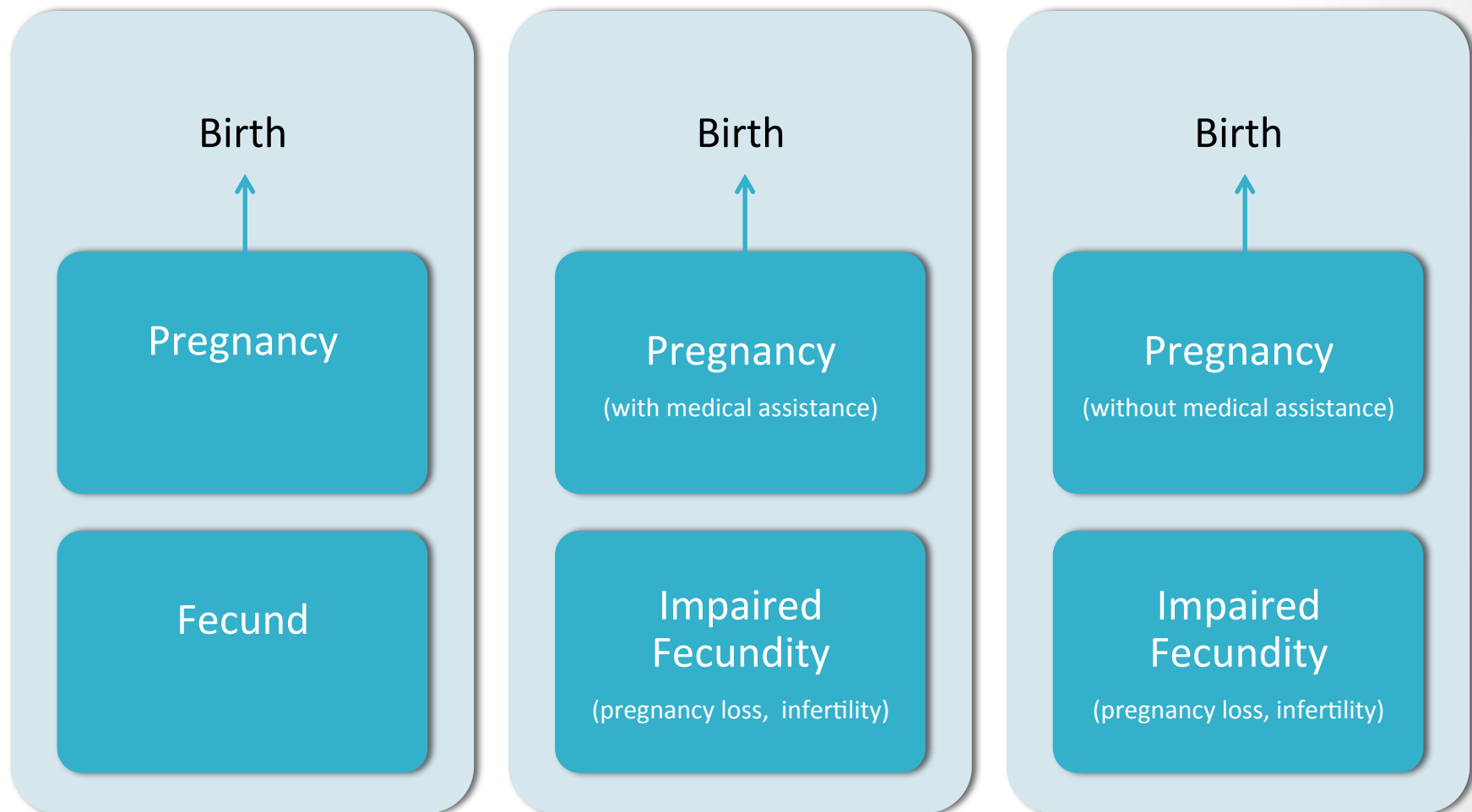
- Biologic capacity for human reproduction irrespective of pregnancy intentions

- **Fertility**

- Demonstrated fecundity as measured by live (still) births



Dynamic Nature of Fecundity and Fertility



Infertility

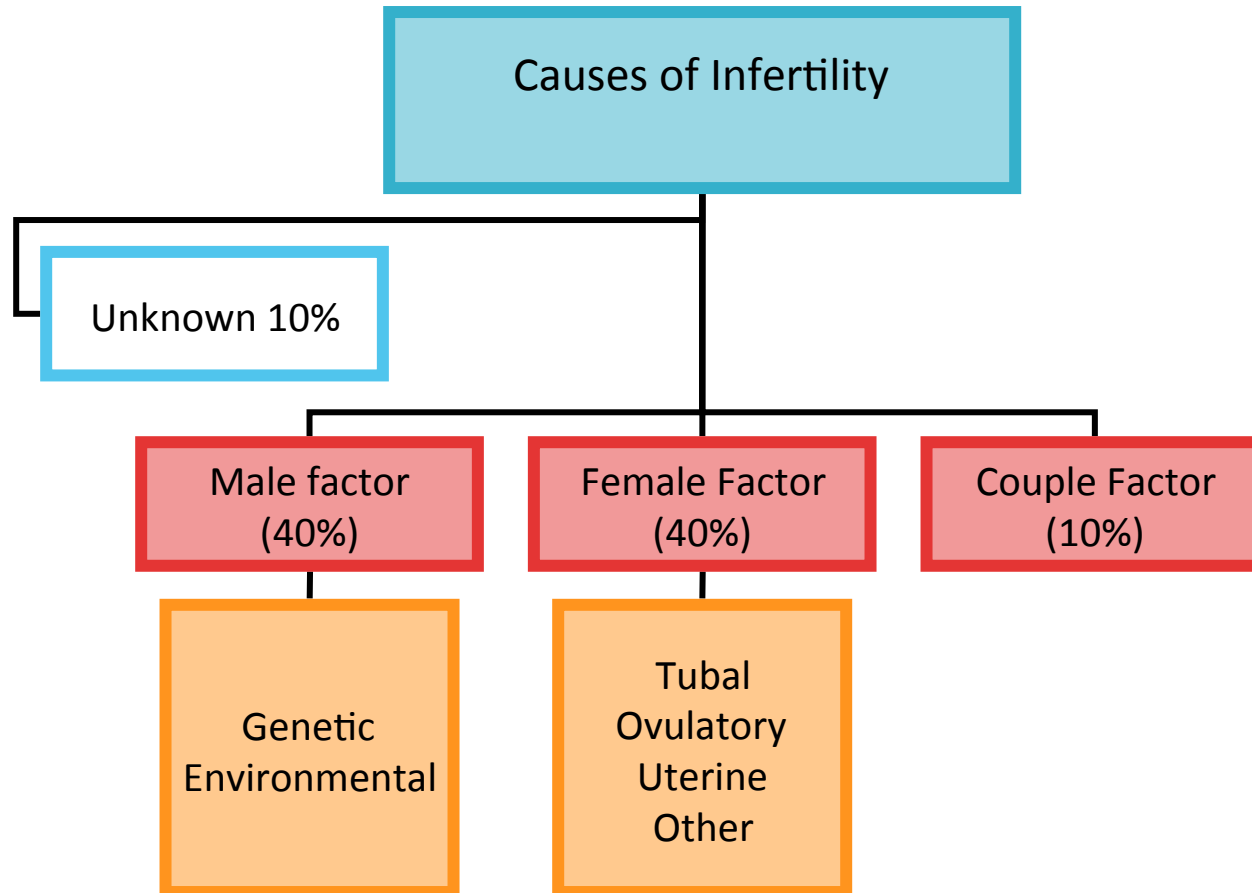
1°

Inability to conceive among couples who have never been pregnant.

2°

Inability to conceive or carry a pregnancy to term among couples with a previous pregnancy regardless of outcome.

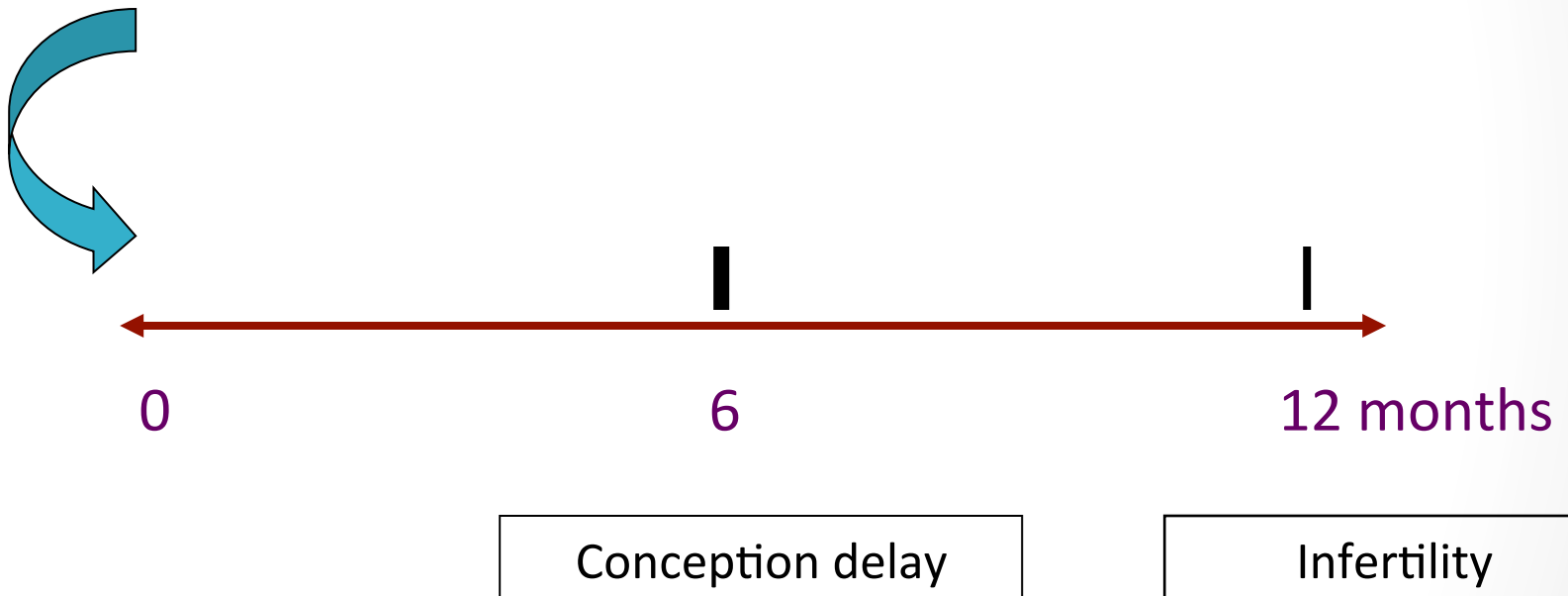
Diagnostic Subtypes of Infertility



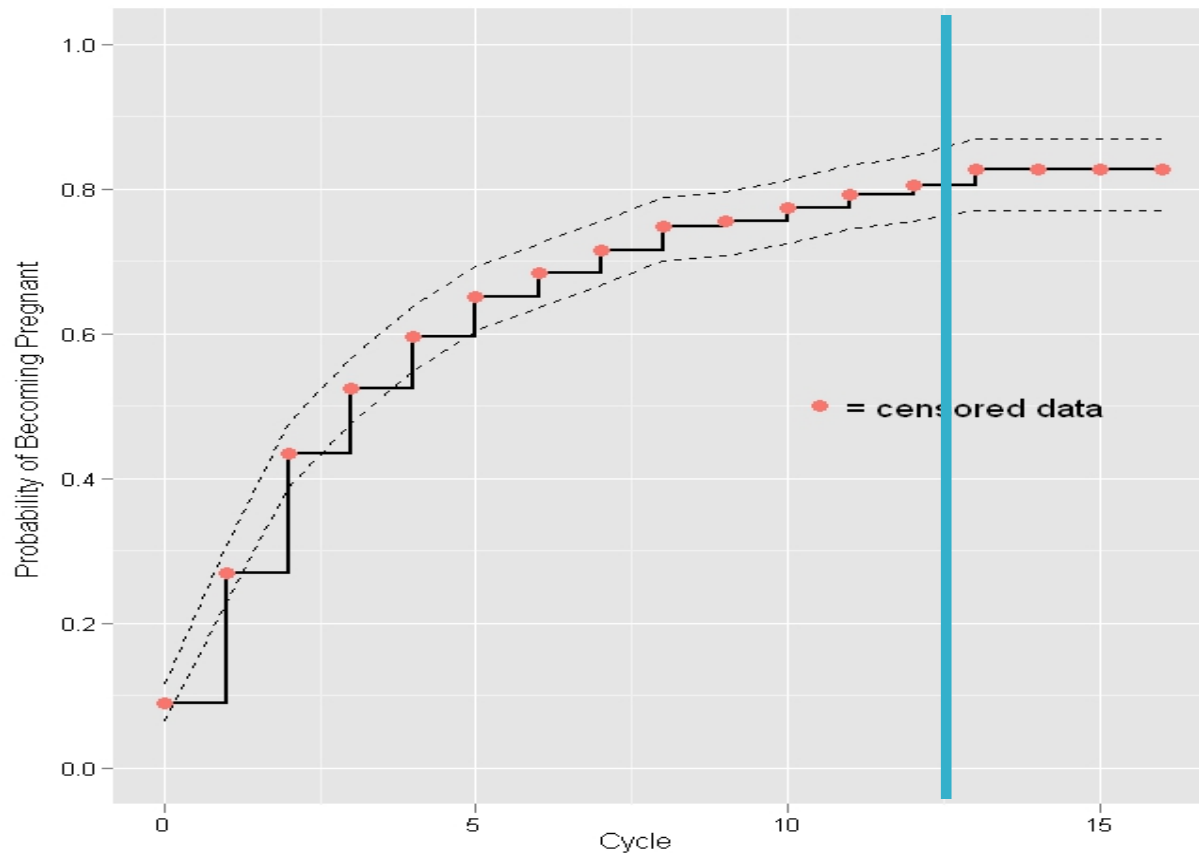
Prior to 1950s, infertility viewed as a “female” problem.

Time-to-Pregnancy

Couples trying (or at risk) for pregnancy



Cumulative Probability of Pregnancy



Buck Louis et al. 2012

TTP Determinants*

Females

- Smoking
- Alcohol
- Caffeine
- BMI (lean & obese)
- Chemicals
- Stress

Males

- Smoking
- Alcohol
- Caffeine
- BMI (lean & obese)
- Chemicals

Swedish women born 1960 or later, 14% TTP explained by OC use prior to attempting, menstrual cycle length, age, & parity
(Axmon et al. 2006)

*Augood et al. 1998; Baird & Strassman 2000; Sharpe & Franks 2002; Hassan & Killick 2004

Validity of TTP (in months)*

| | |
|-------------------------|------------|
| Exact Agreement | 17% |
| <u>±</u>1 months | 41% |
| <u>±</u>2 months | 65% |
| <u>±</u>3 months | 72% |

*33% of women could not remember

Infertility

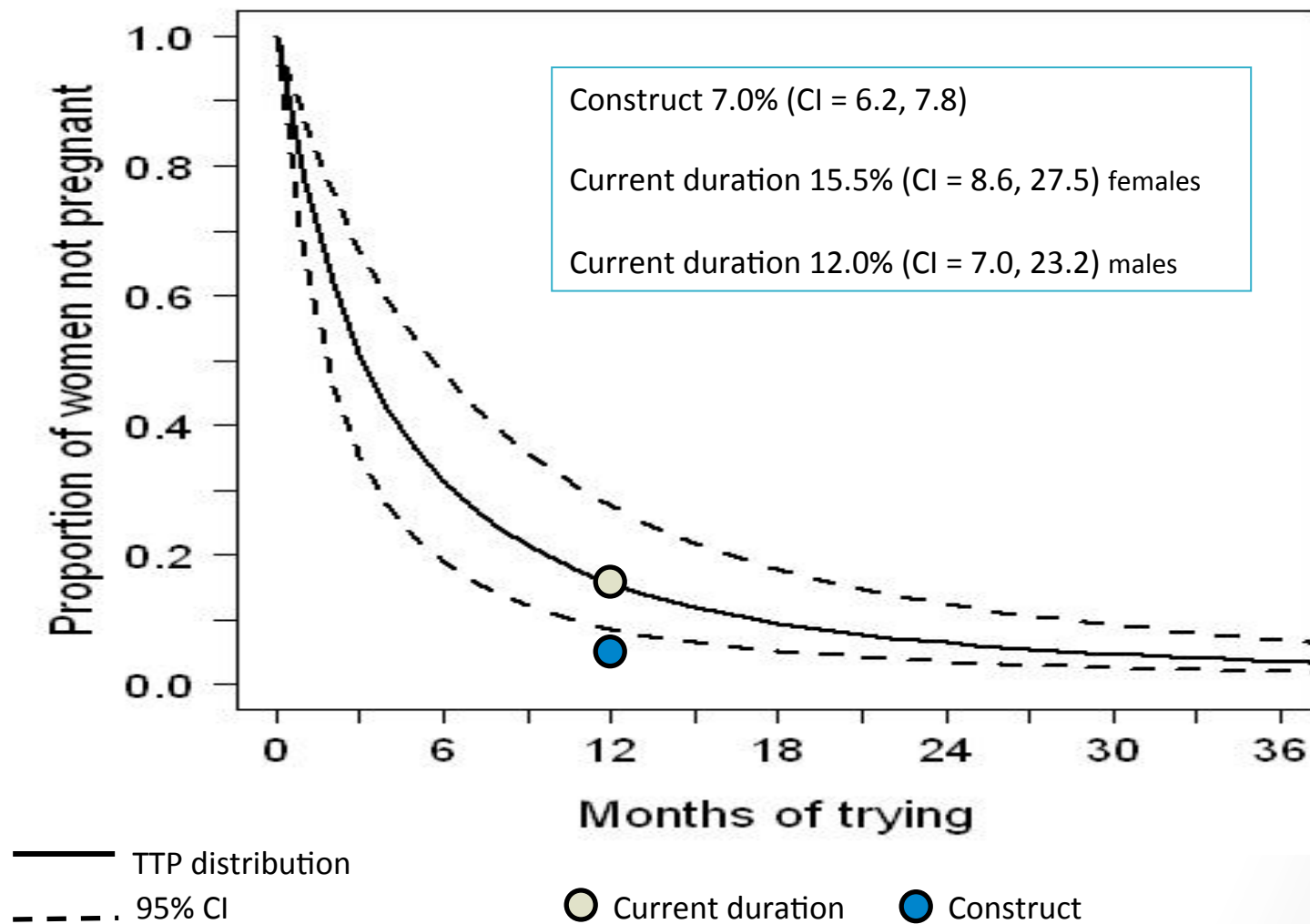
Incidence & Prevalence



Infertility - Globally

- Incidence uncertain
 - 12% - 18% prospective cohorts (preconception enrollment)
- Global Prevalence \approx 15%
 - 4 - 14% Germany (Schmidt et al. 1995)
 - 6% - 20% European populations (Karamus et al. 1999)
 - 6% - 12% Tanzania (Larsen 2005)
 - 7% - 9% developing countries (Boivin et al. 2007)
 - 8% - 12% Asia & Latin America (WHO 1991)
 - 9% - 30% Sub-Saharan Africa (Sundby et al. 1998; Geelhoed et al. 2002; Okonofua 1996)

Estimated U.S. Infertility Prevalence by Method



Thoma et al. 2013; Louis et al 2014

% Women Failing to Conceive by Male's Age*

| Male Age (in years) | % Women aged 35 yrs. Without Conception |
|---------------------|---|
| <35 | -- |
| 35 | 18 |
| 40 | 28 |

*Within 12 cycles. European Fecundability Study (Colombo & Masarotto 2000; Dunson et al. 2004)

% Women Failing to Conceive Within 12 Cycles

| Female Age (in years) | % |
|-----------------------------------|-------|
| Intercourse - twice weekly | |
| 19-26 | 8 |
| 27-34 | 13-14 |
| 35-39 | 18 |
| Intercourse – once weekly | |
| 19-26 | 15 |
| 27-34 | 22-24 |
| 35-39 | 29 |

European Fecundability Study (Colombo & Masarotto 2000; Dunson et al. 2004)

Analytic Epidemiology

■ Female Infertility

- Age
- Medical history
- Environment
 - Lifestyle
 - Diet
 - Occupation & hobbies
 - BMI
 - Stress

■ Male Infertility

- Age
- Medical history
- Environment
 - Lifestyle
 - Diet
 - Occupation & hobbies
 - BMI

Male Biological Clock



- Androgen production & spermatogenesis continues over lifespan, though not at same capacity
 - Aging of testes, accessory glands, epididymis
 - ↓ spermatogenesis & Leydig cell function
 - ↓ blood testosterone $\approx 1\%$ per year at 30 years (Pasqualotto et al. 2004; Feldman et al. 1994)

- Advancing paternal age associated
 - Miscarriage (Dunson et al. 2002)
 - Autism spectrum disorder (Reichenberg et al. 2006)
 - Schizophrenia (Malaspina et al. 2001)
 - Down Syndrome (Fisch et al. 2003)

... fecundity impairments & health

Male Fecundity & Later Onset Adult Disease*

| Fecundity Marker | Adult Disease |
|------------------|---|
| GU malformations | Poorer semen quality |
| GU malformations | > Risk testes cancer |
| Semen quality | Earlier mortality Offspring at > risk GU malformations |

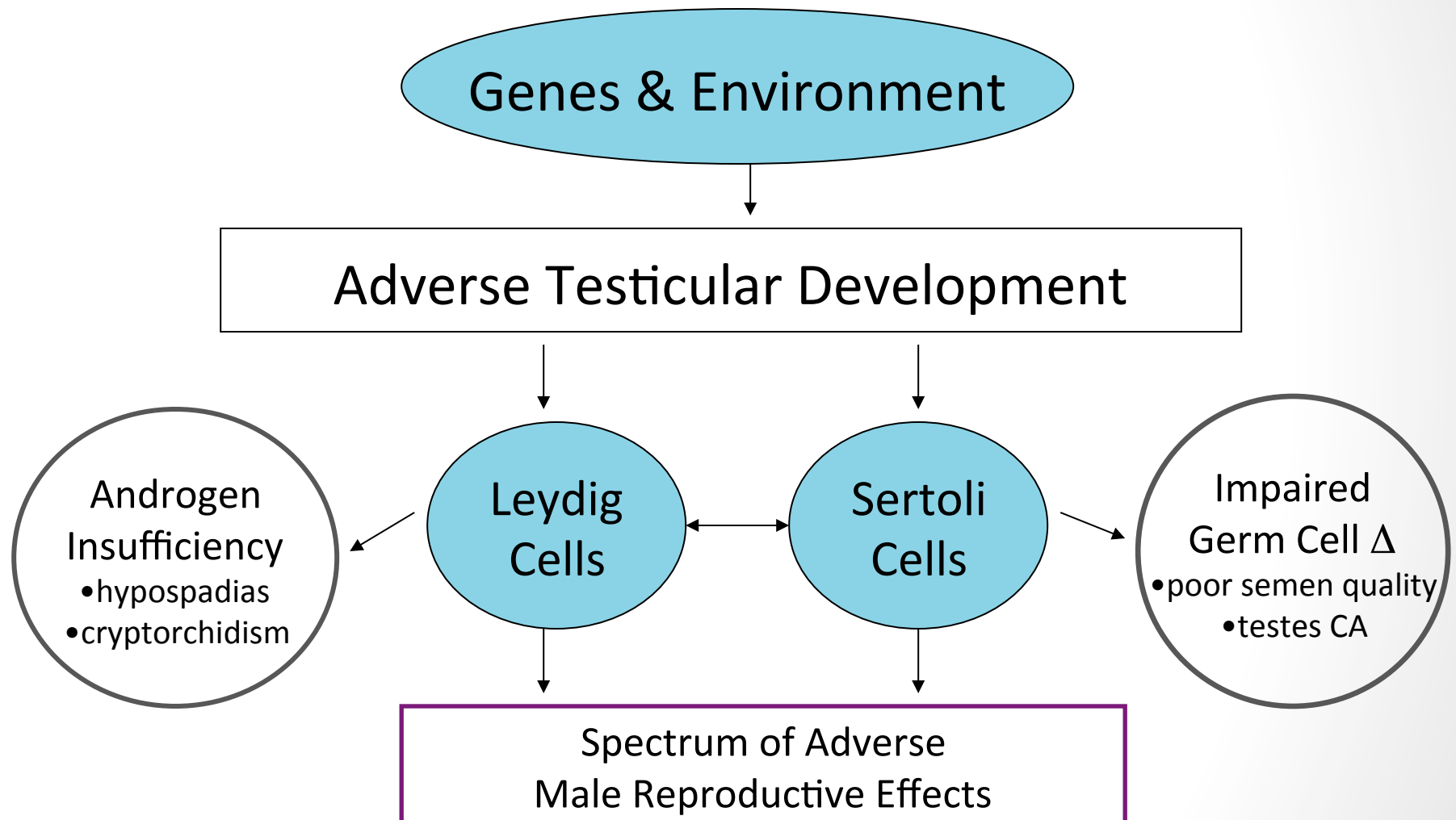
*Observational studies

Female Fecundity & Later Onset Adult Disease*

| Fecundity Marker | Adult Disease |
|---|---|
| <i>In utero</i> growth restriction | Earlier puberty, higher risk GDM, earlier menopause |
| Earlier menarche, later menopause, nulliparity, PCOS, pre-eclampsia | > Risk cancer |
| GDM, PCOS | > Risk CHD, T2D, metabolic syndrome, stroke, endometrial cancer |
| Endometriosis | > Autoimmune disorders, cancer risk (reproductive sites) |

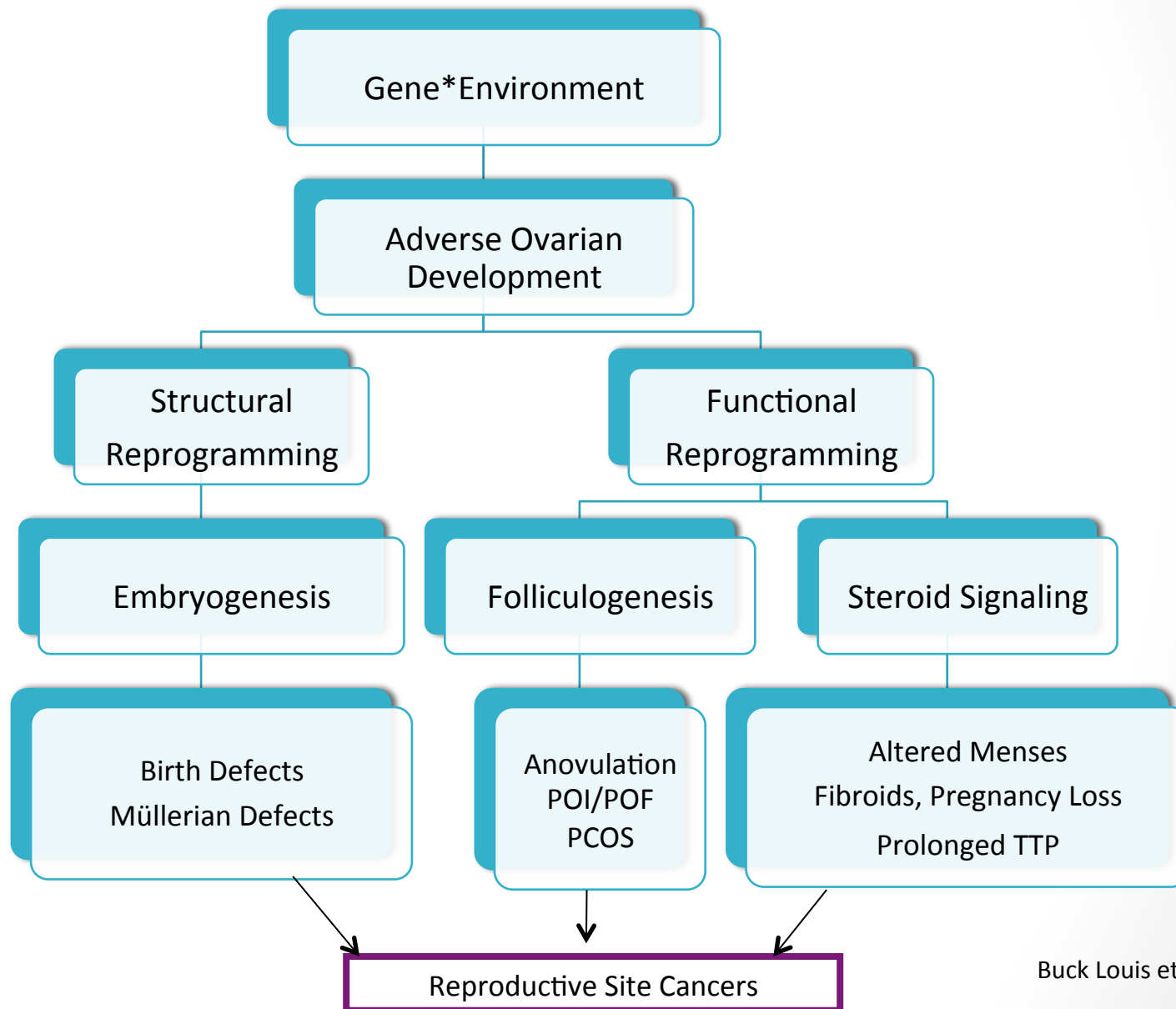
*Observational studies

Testicular Dysgenesis Syndrome (TDS)



*Skakkebaek et al. 2001

Ovarian Dysgenesis Syndrome (ODS)



Critical Tipping Point*

- Historically low fertility rates in many industrialized countries
 - Levels < required for sustaining populations (Lutz et al. 2003)
- Hypothesized large role for male subfertility associated with ↑ testes CA
 - ‘Whistleblower’ for subfertility (Skakkebaek et al. 2006, 2007)
- Rapid changes suggest environmental influences; few genetic causes (Y chromosome deletions)

*Andersson et al. 2008

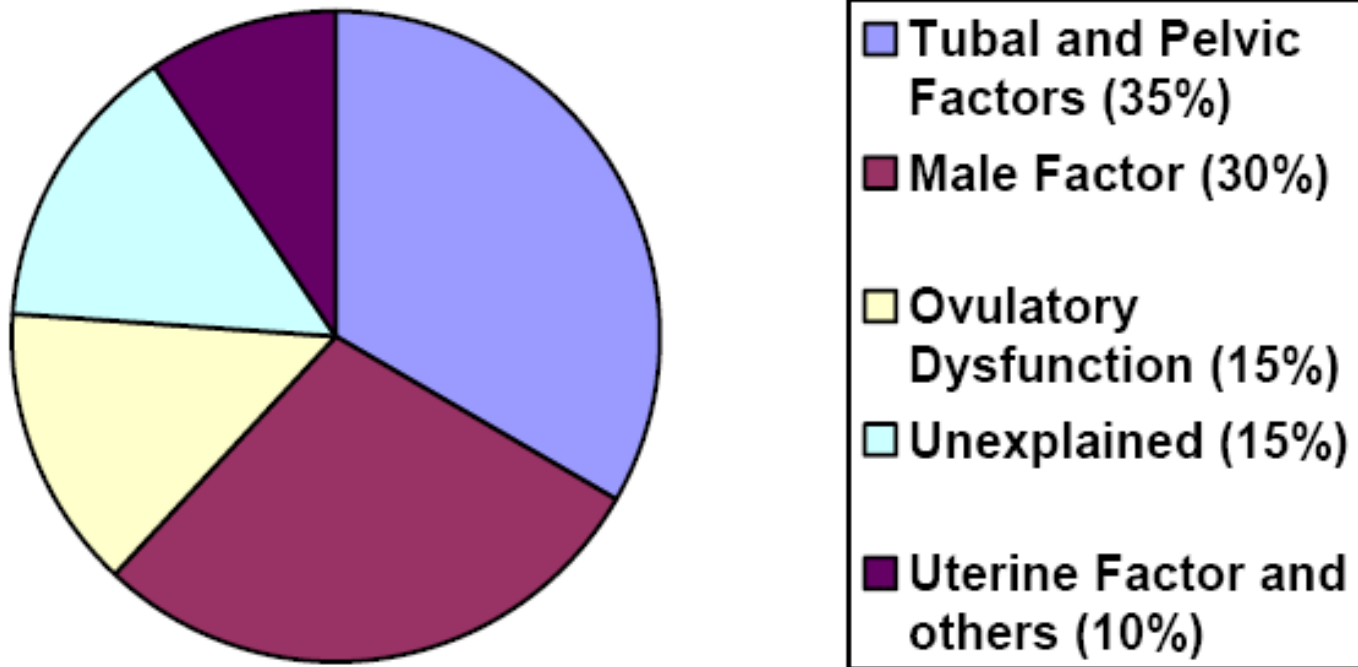
Clinical Approach to Infertility: Diagnosis & Management

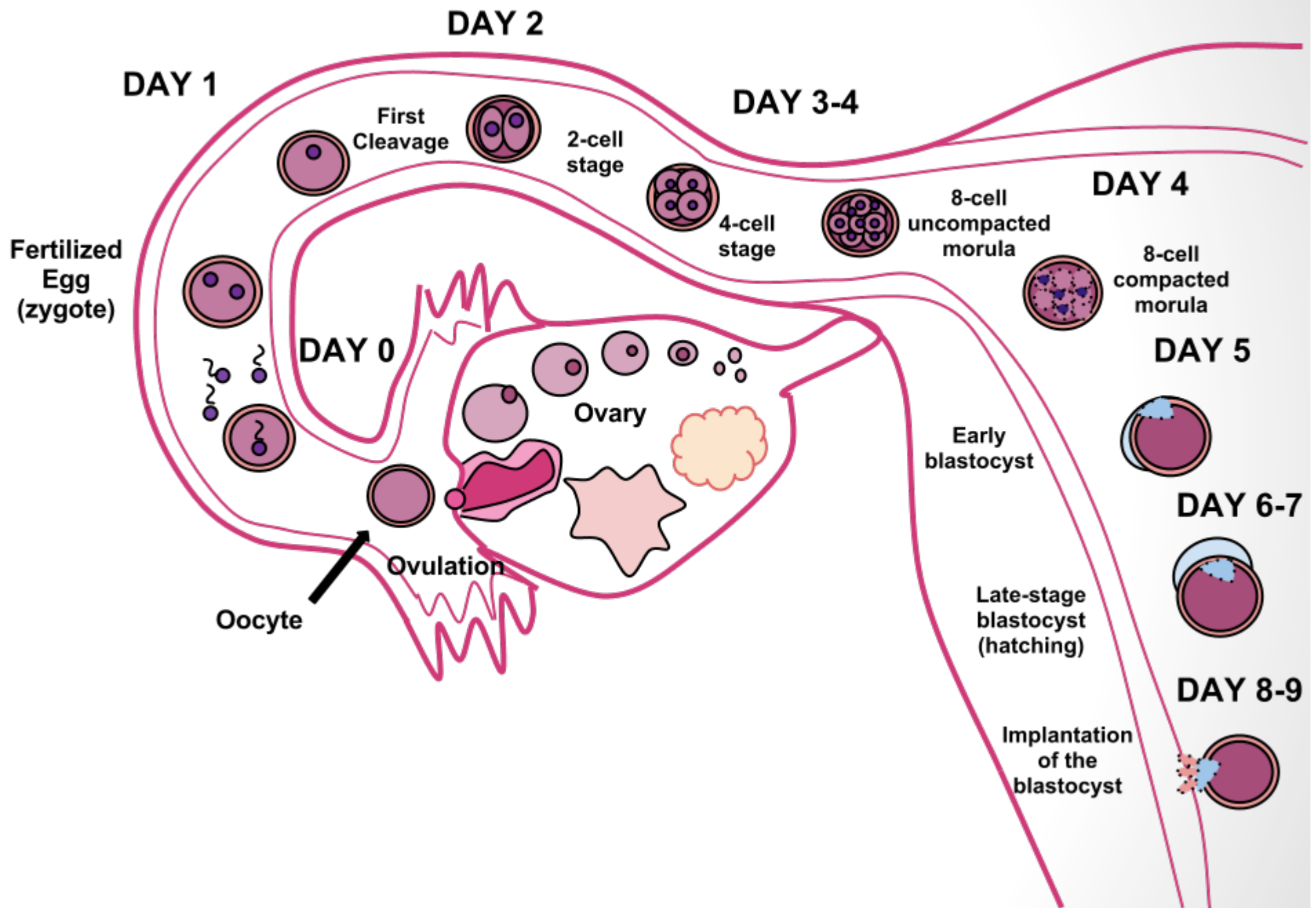


Infertility is a Disease

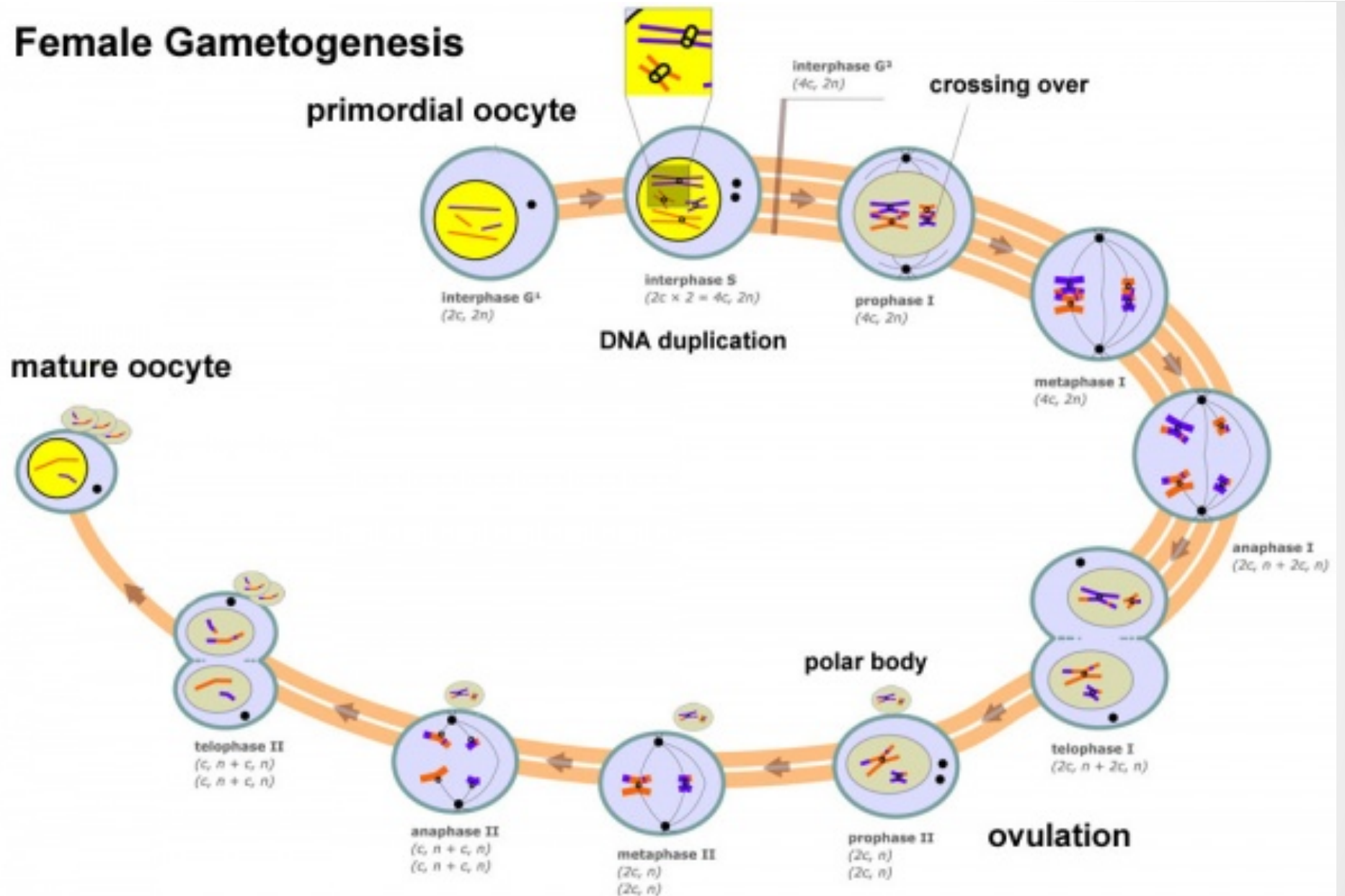
- Inability to conceive after 1 year of intercourse without conception (American Fertility Society 1991)
- A disease resulting in abnormal reproductive function (American Fertility Society 1990)

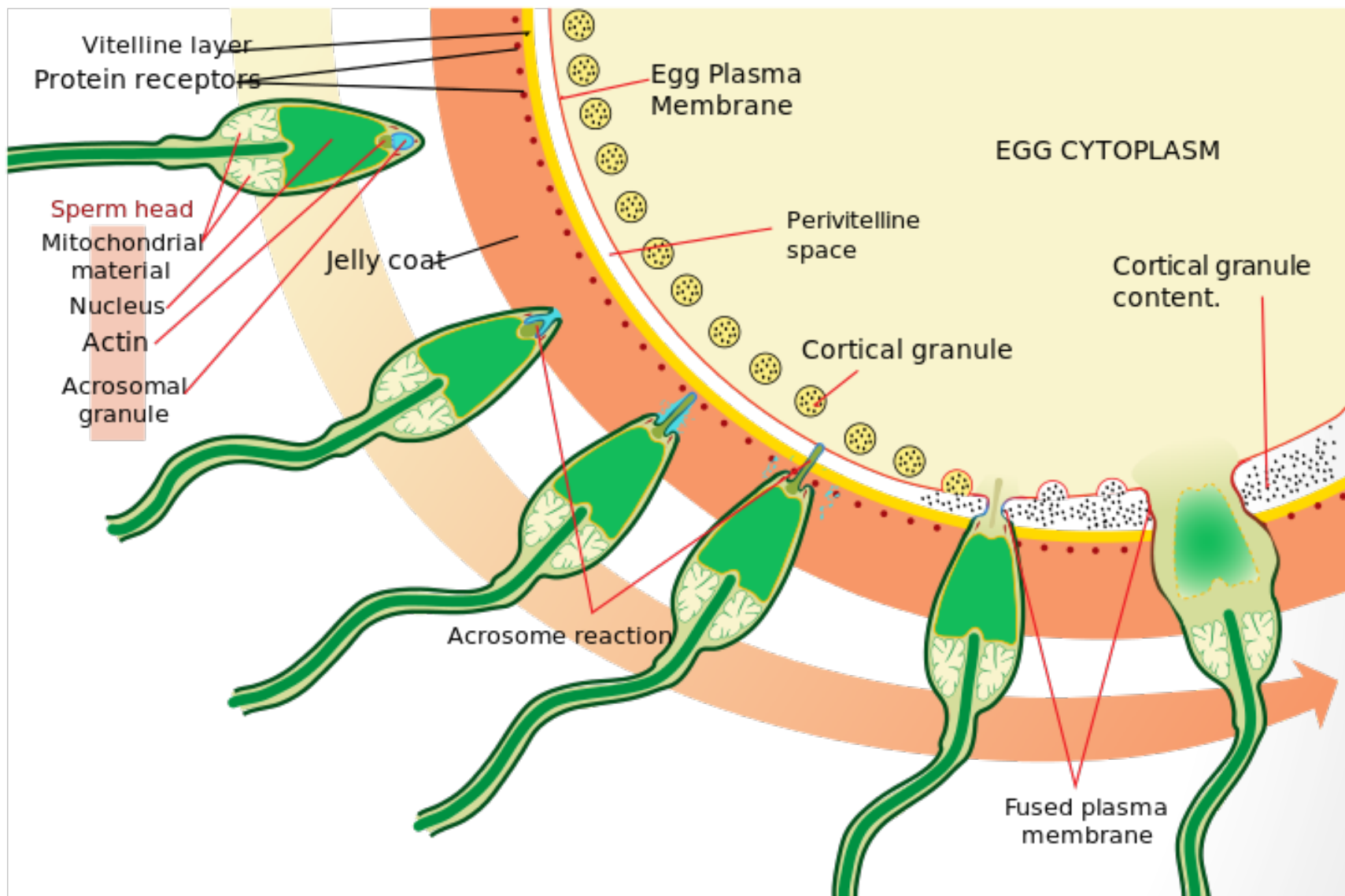
Infertility Causes in Couples



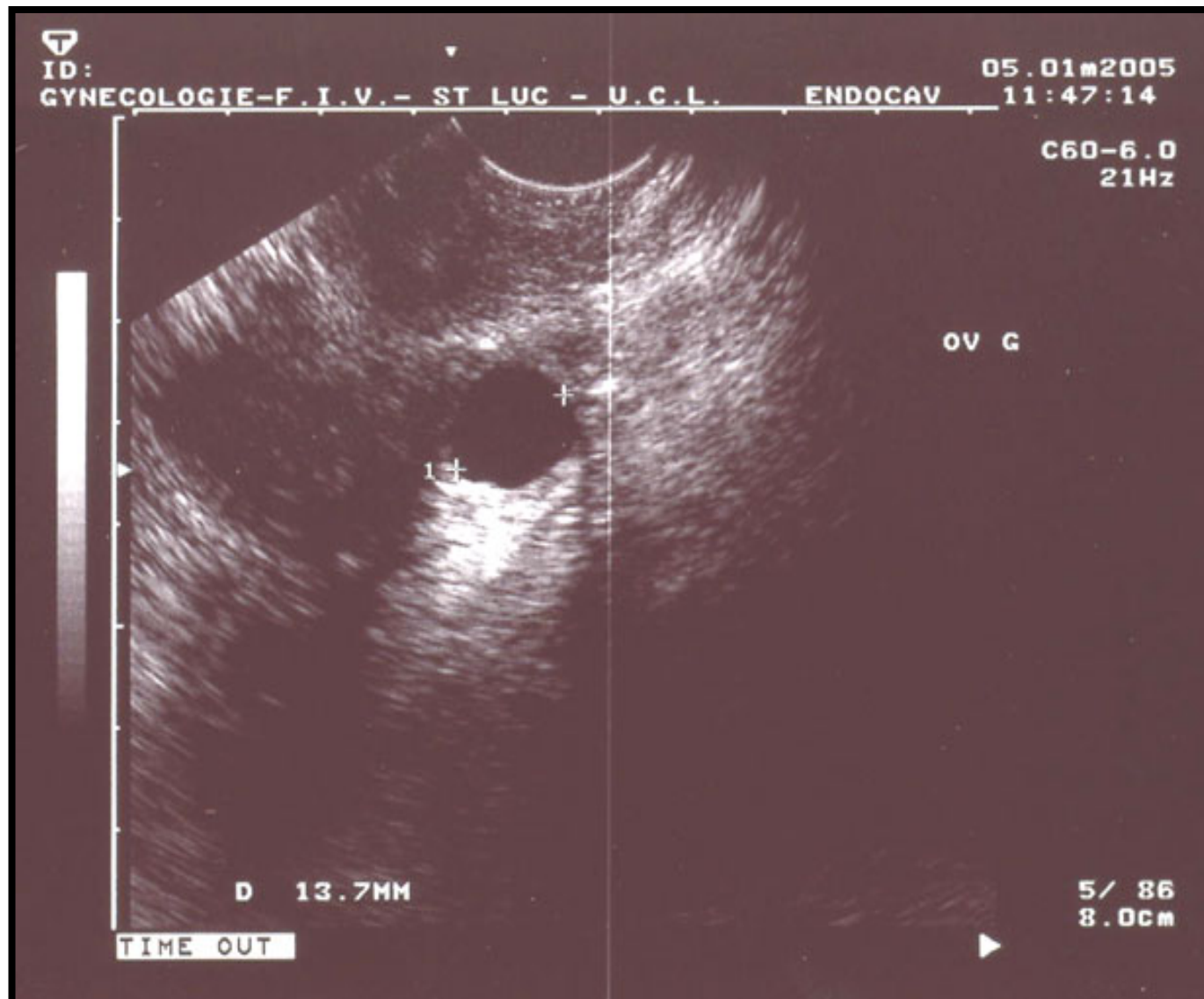


Female Gametogenesis

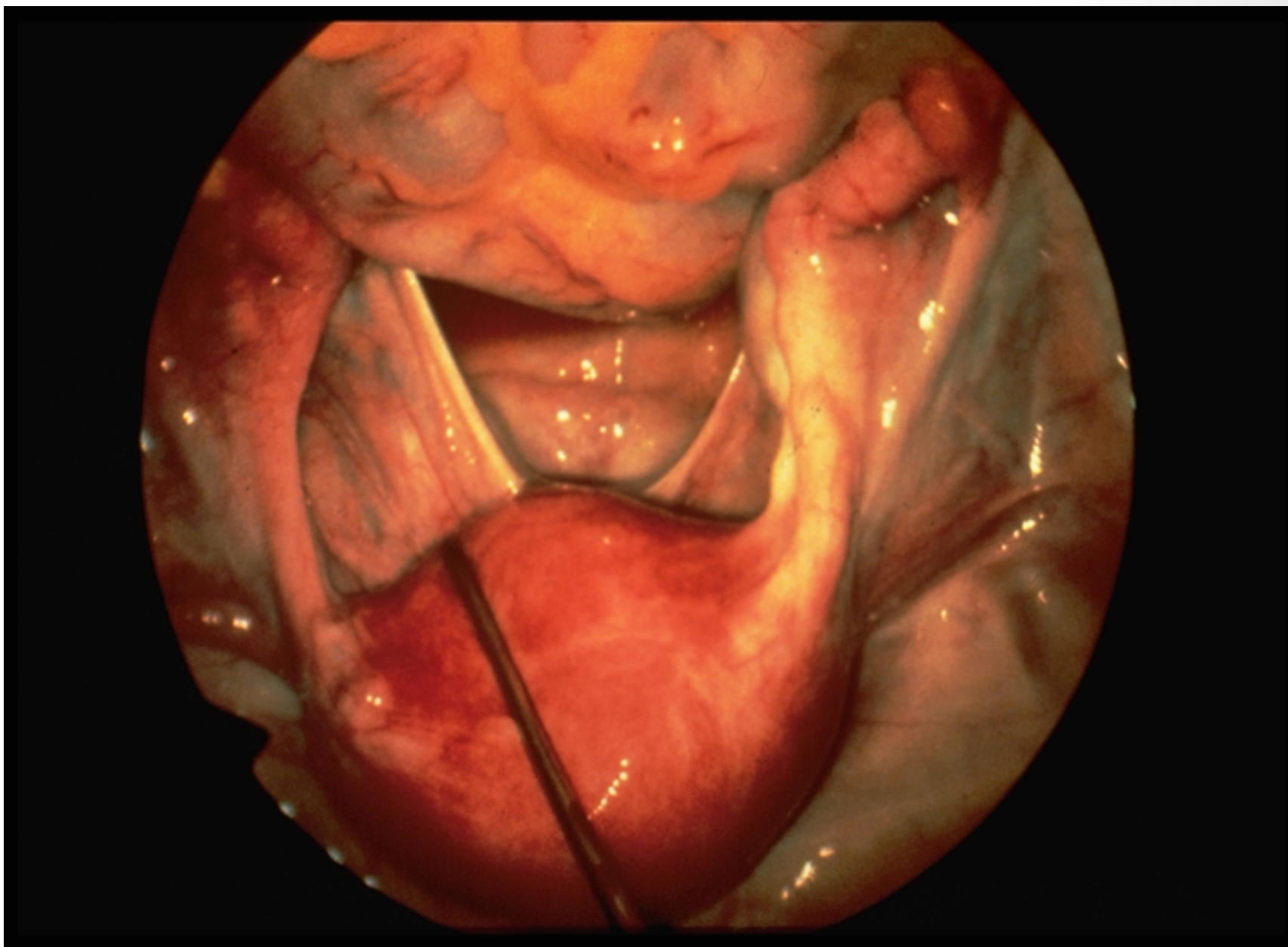




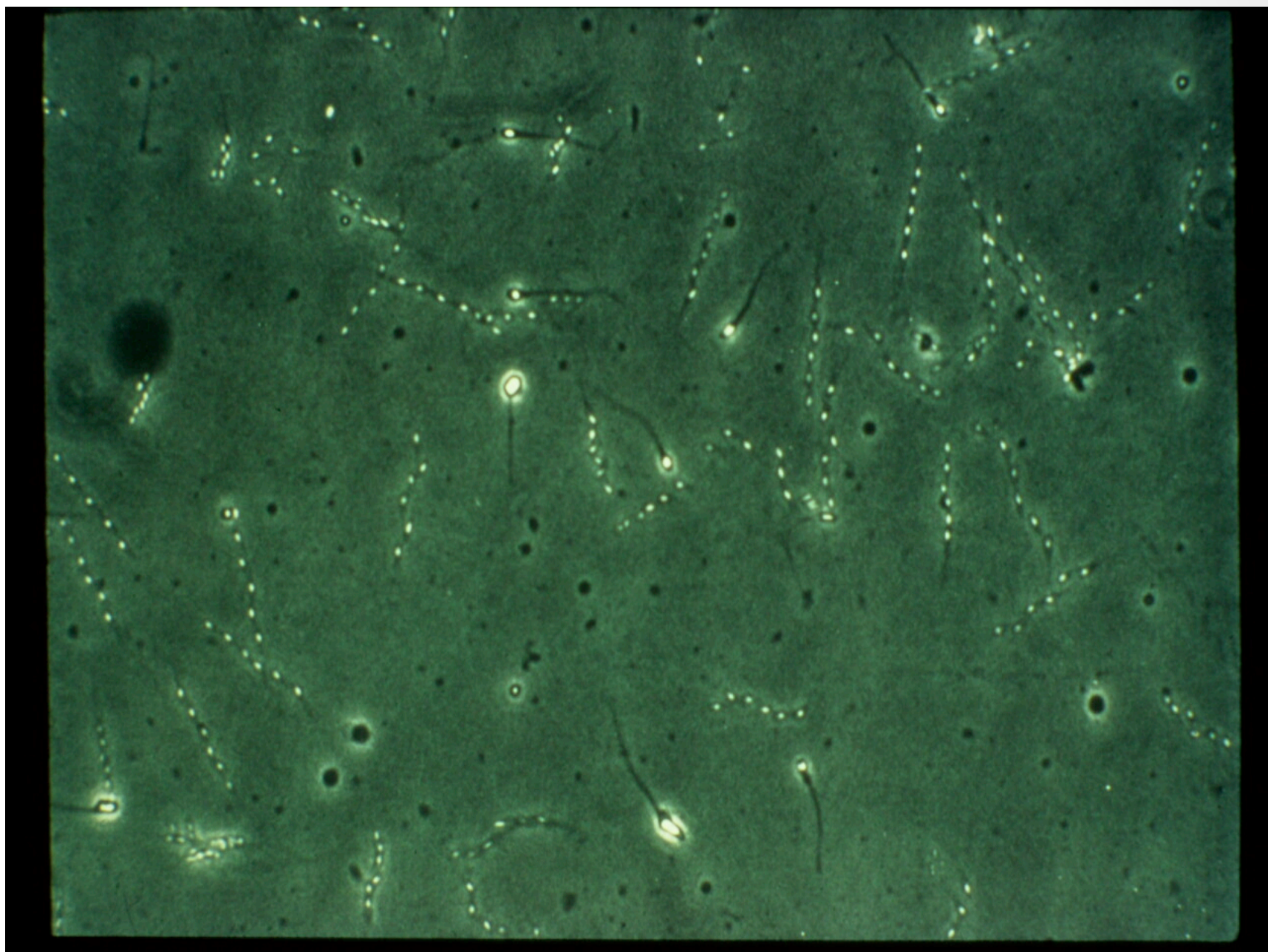
Follicle
05.01.2005 - 13.7 mm

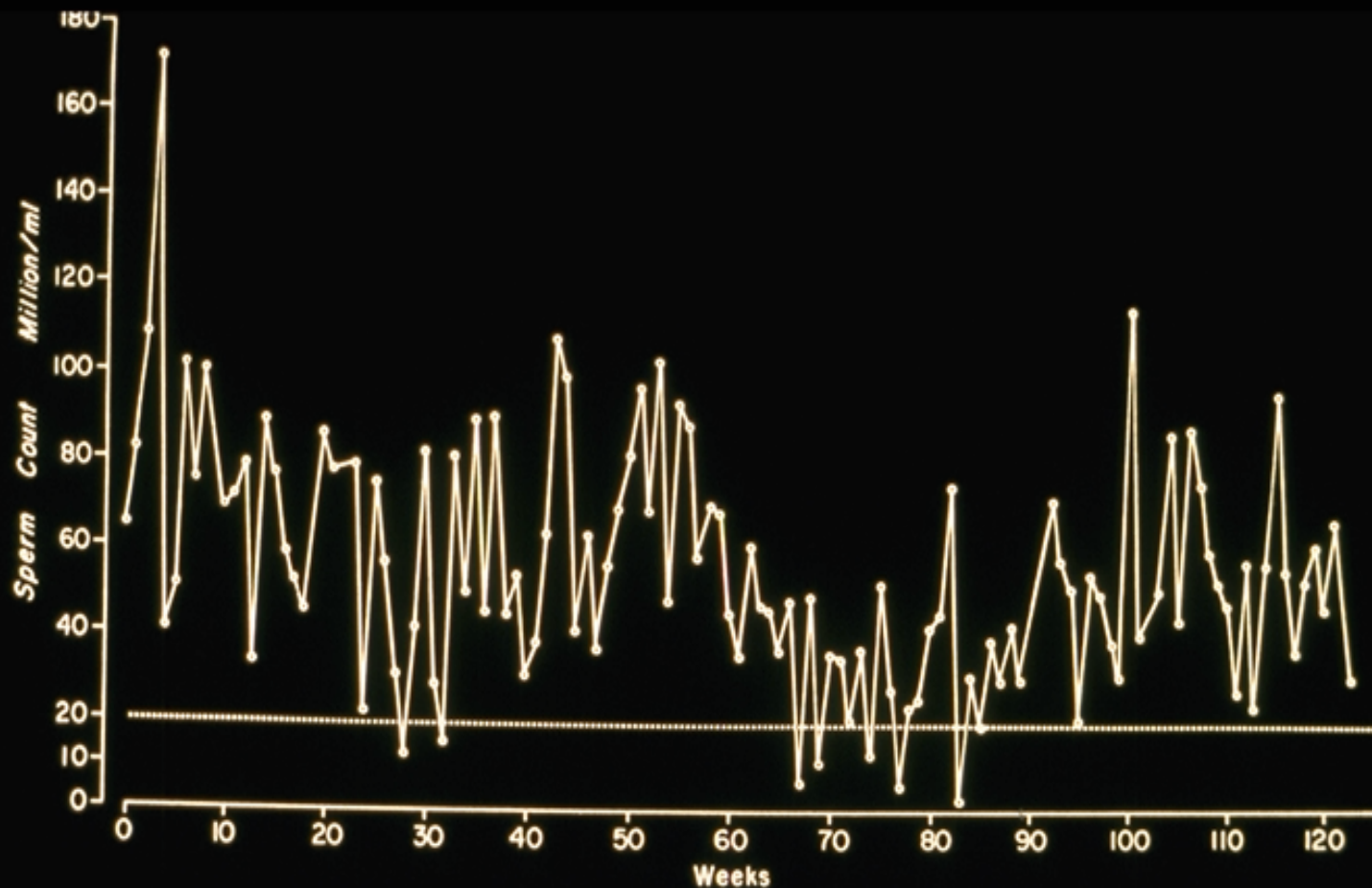


MMY



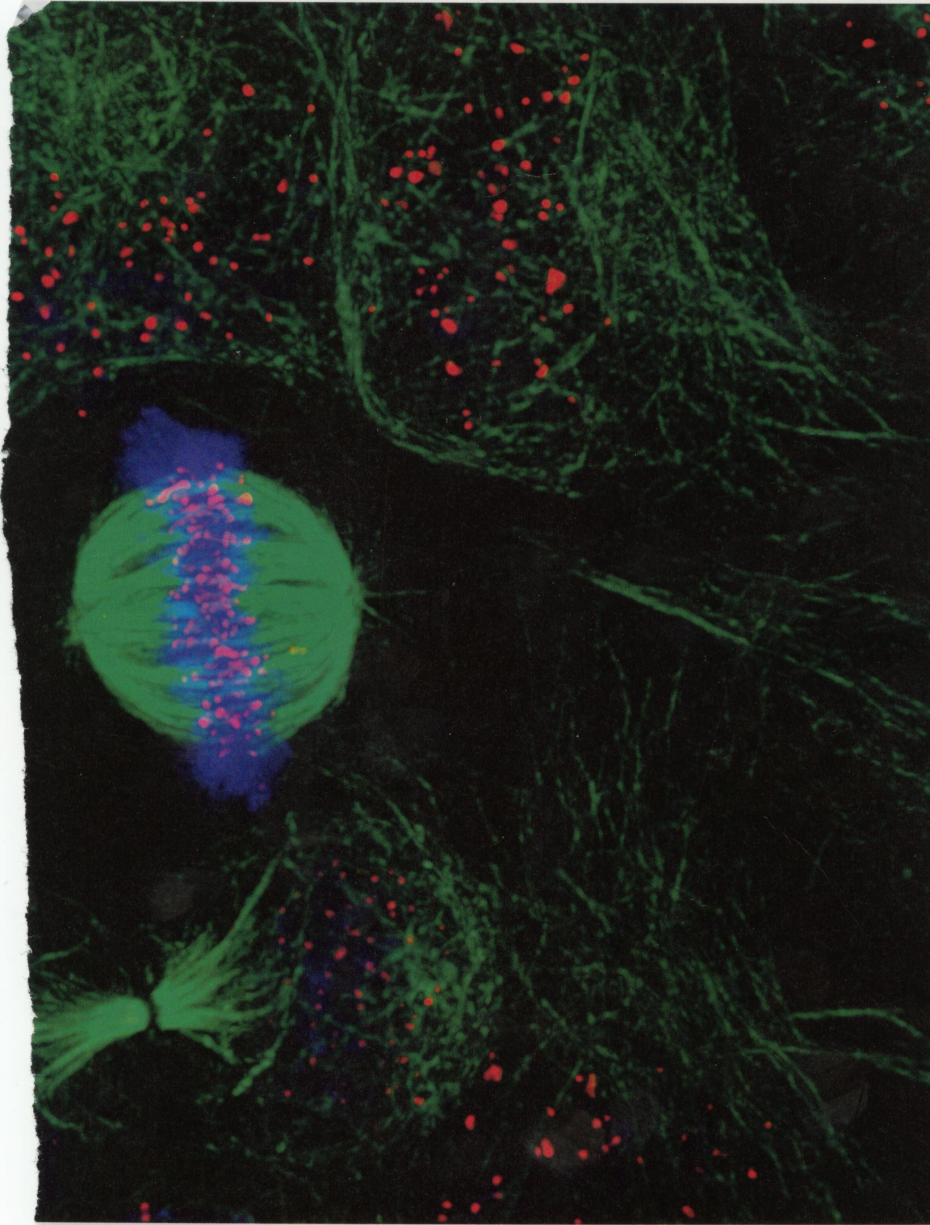






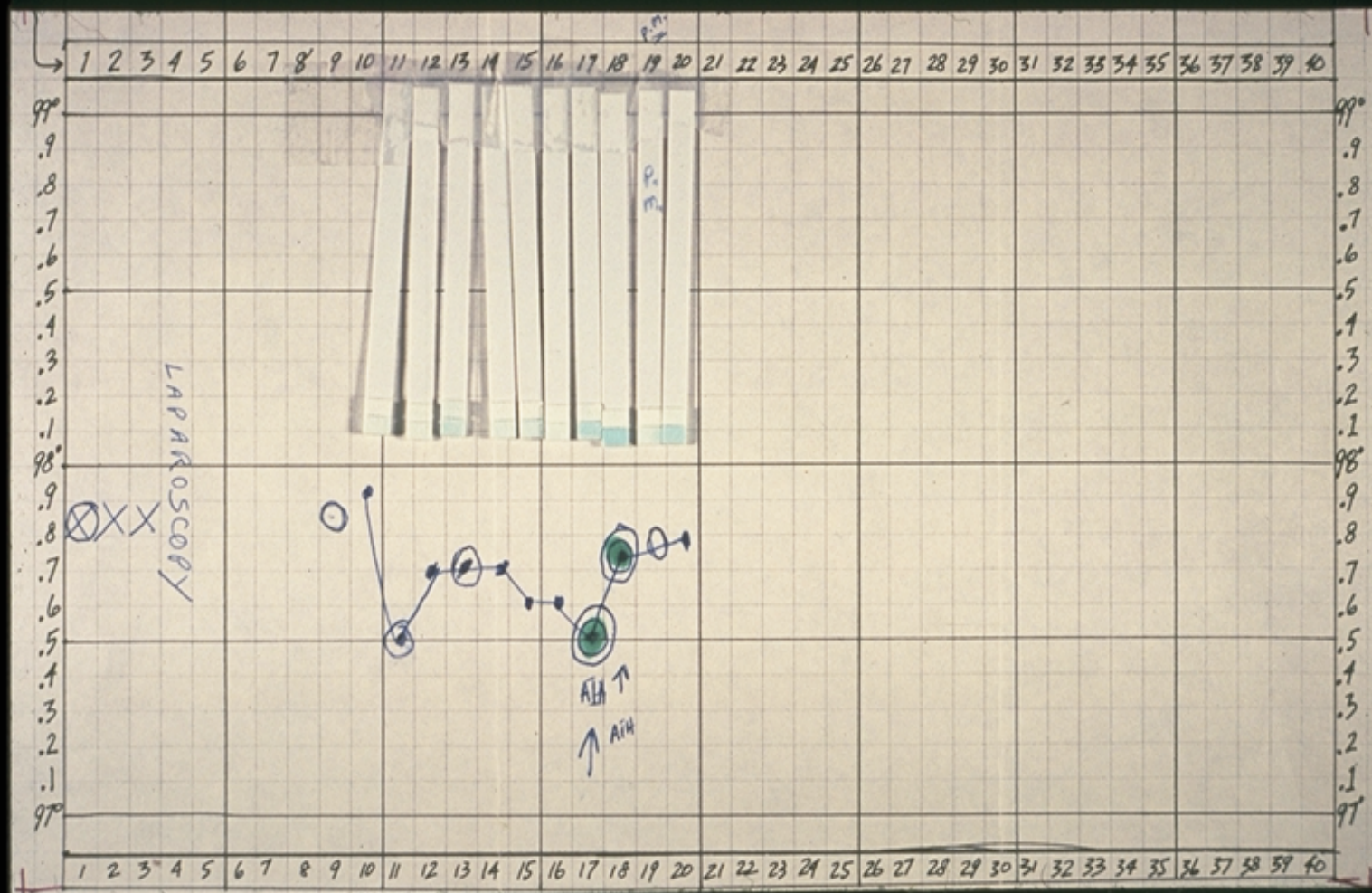
Biweekly seminal fluid sperm concentrations from one individual over a period of 120 weeks. During this period the individual received no medication and reported no periods of febrile illness. Dotted line indicates 20 million/ml which is generally considered to be the lower limit of normal range (see 2.9 paragraph 3). Unpublished data from Dr C.A. Paulsen.

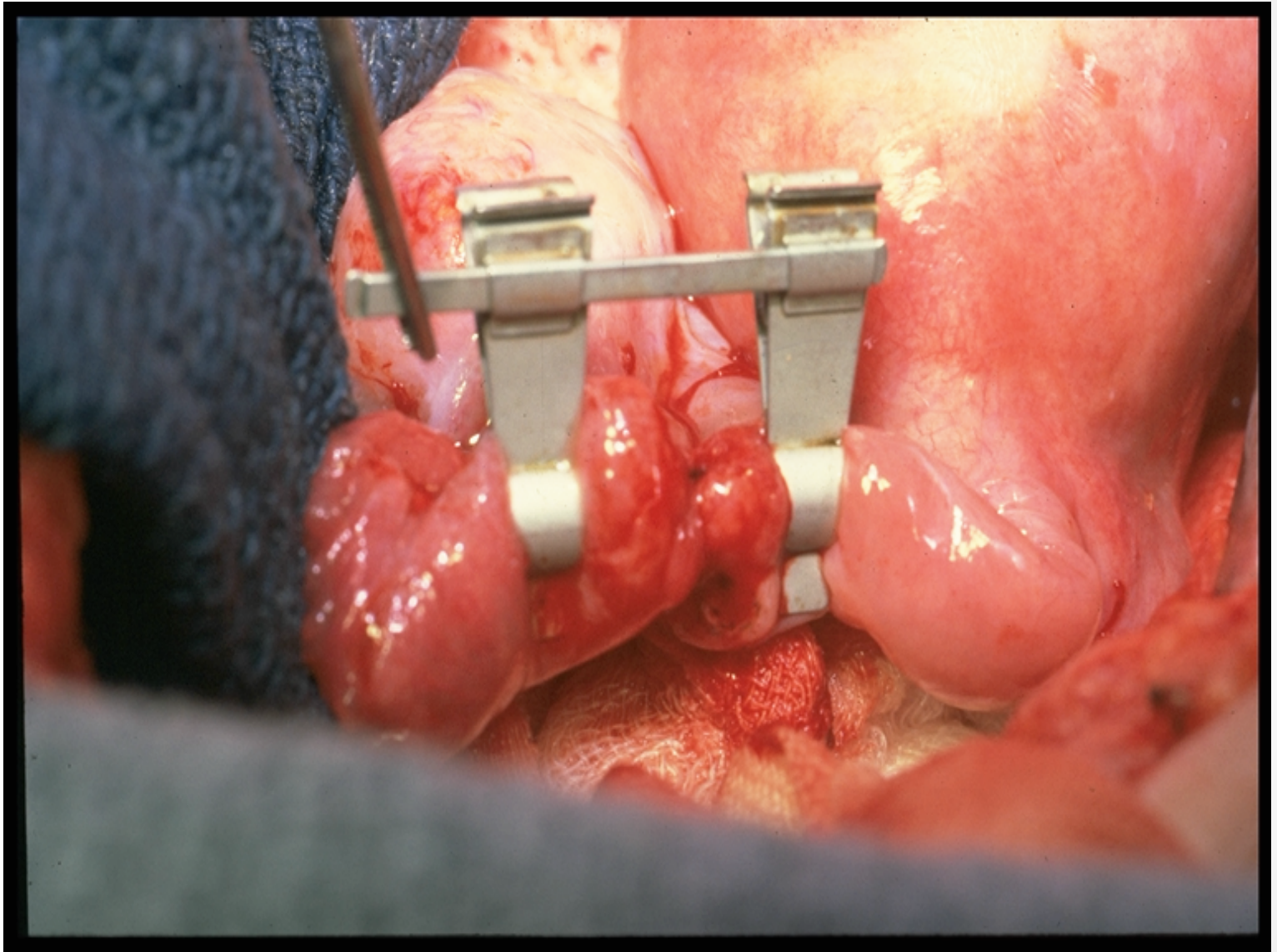




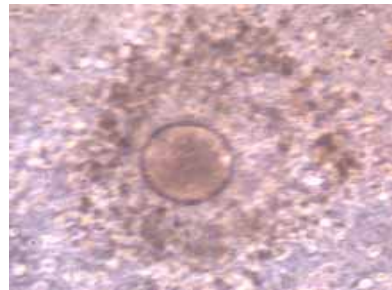
Miscarriage and Maternal Age

| Age (years) | Total number of pregnancies | Miscarriage rate |
|-------------|-----------------------------|------------------|
| 20-24 | 350 395 | 9% |
| 25-29 | 414 149 | 11% |
| 30-34 | 23 5049 | 15% |
| 35-39 | 93 940 | 25% |
| 40-44 | 25 132 | 51% |
| ≥ 45 | 1865 | 75% |

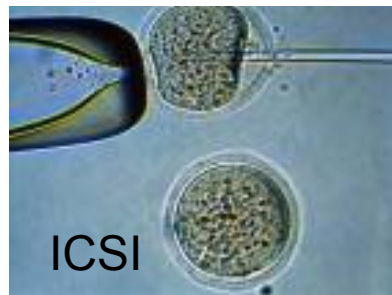




Overview of IVF Procedure: Gametes to Embryo



oocyte



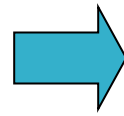
ICSI



sperm



zygote

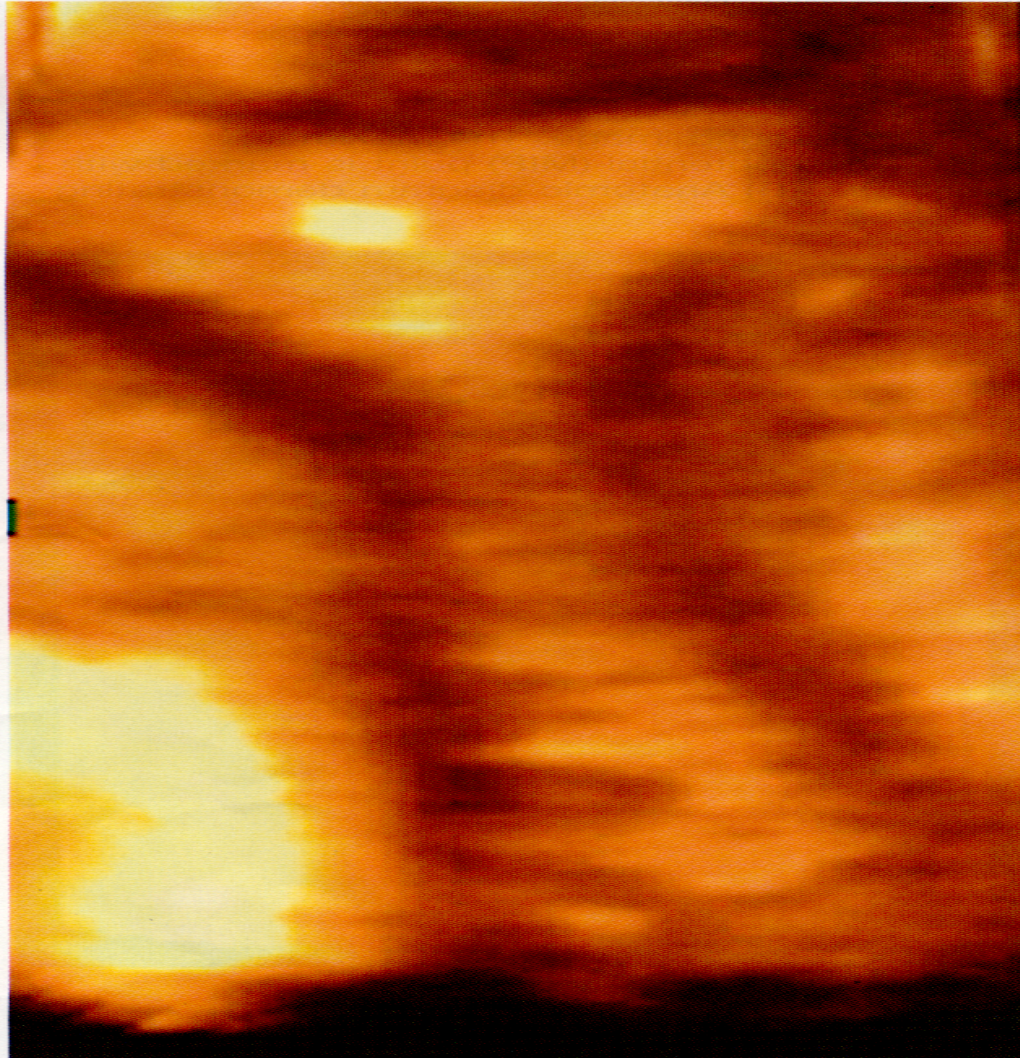


embryo

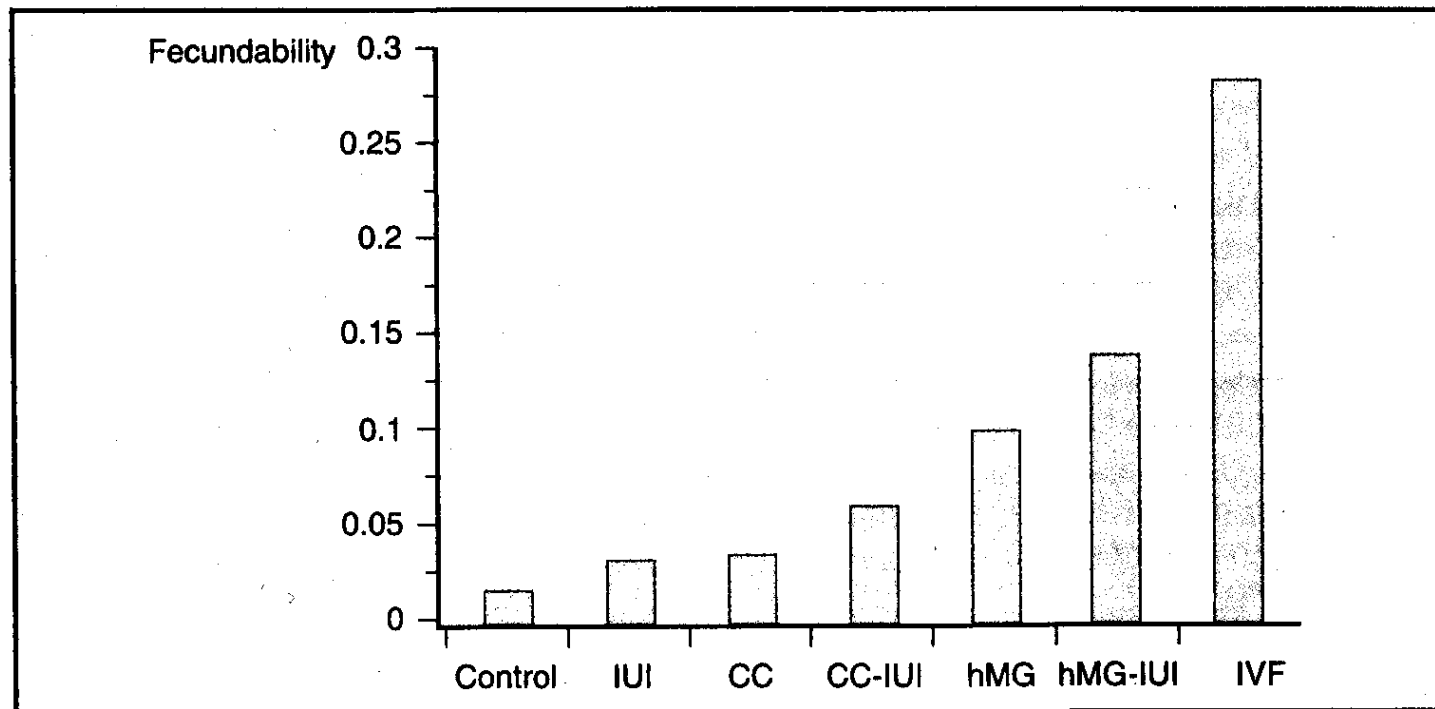


blastocyst

Embryo flash is confirmed on 3D ultrasound after transfer in area of maximal implantation potential.

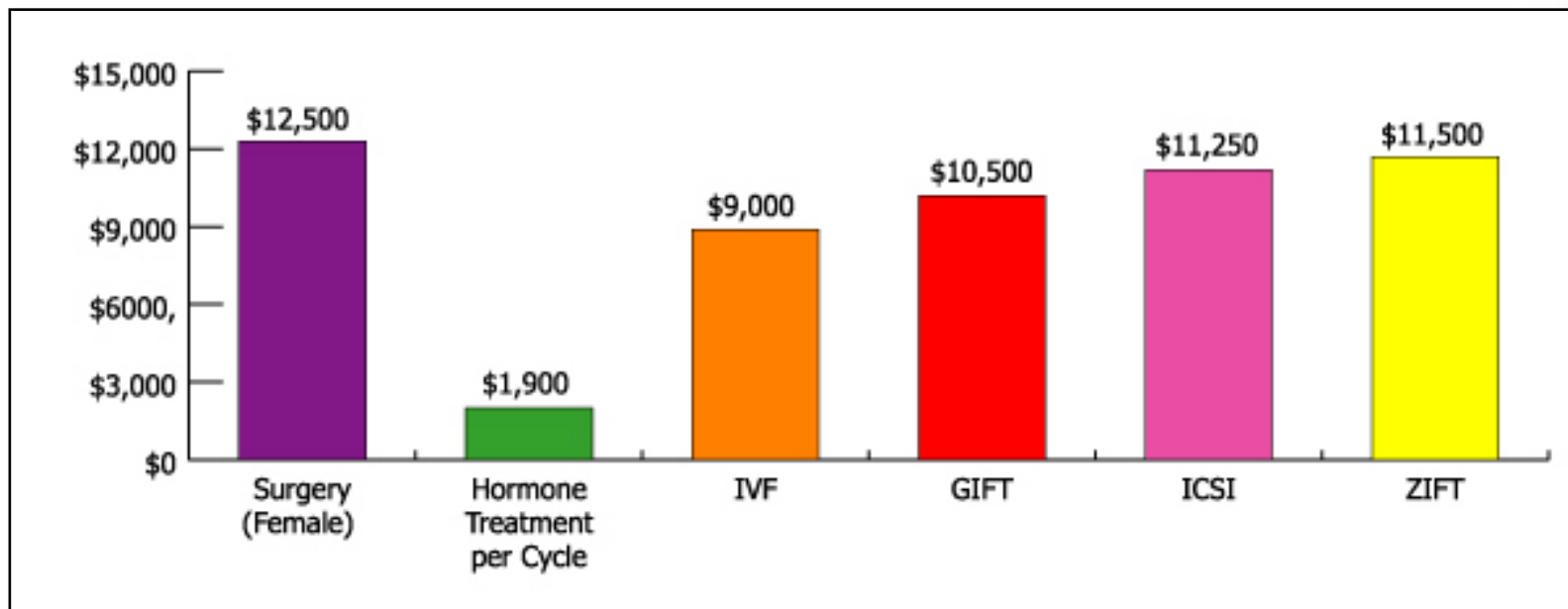


Gergely. Embryo transfer using the 3D/4D ultrasound. Fertil Steril 2005



Infertility Treatment Costs

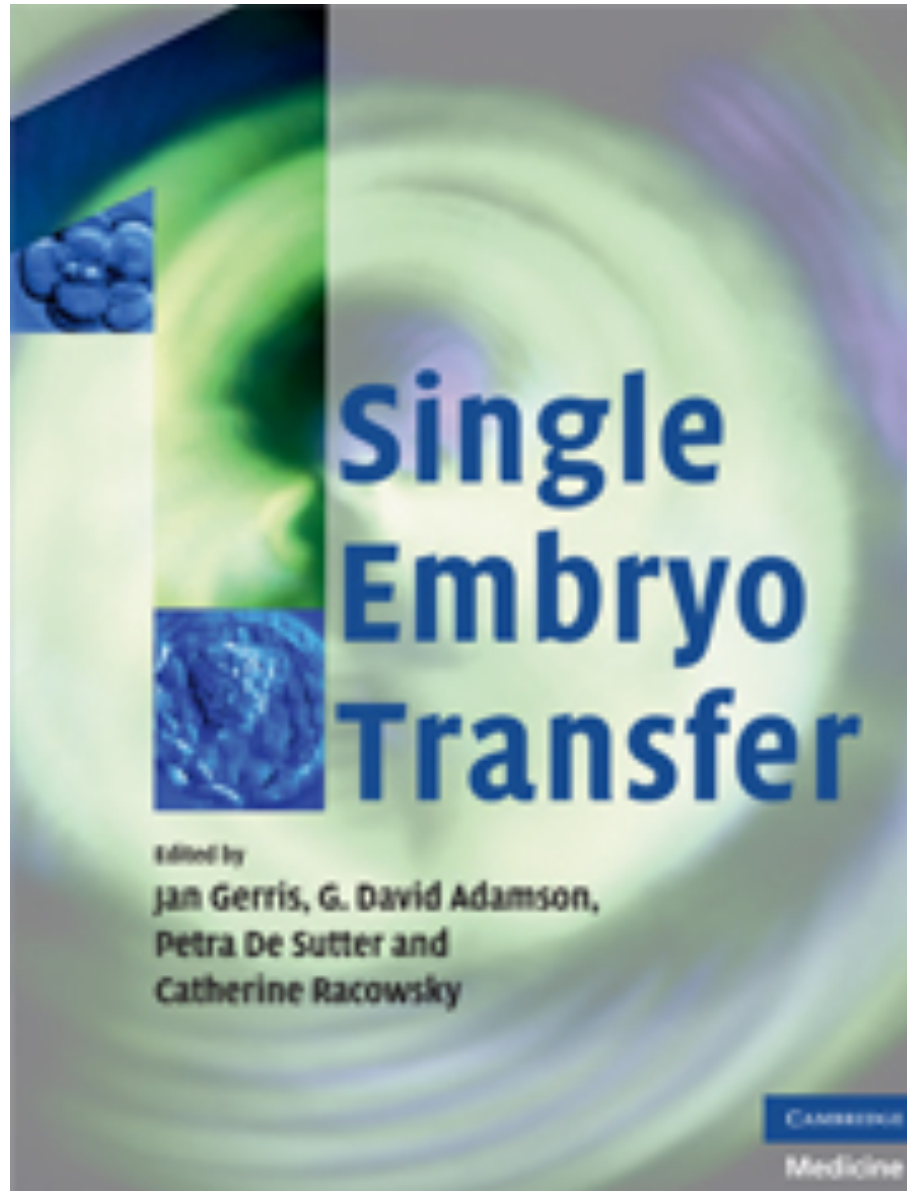
Infertility-related procedures are a more significant cost driver than pharmacotherapy (Davis 1996)



IVF = In vitro fertilization; GIFT = Gamete intrafallopian transfer
ICSI = Intracytoplasmic sperm injection; ZIFT = Zygote intrafallopian transfer

Controversy: What do patients want?

- The desire of infertile patients for multiple births
(Ryan et al. Fertil Steril 2004)

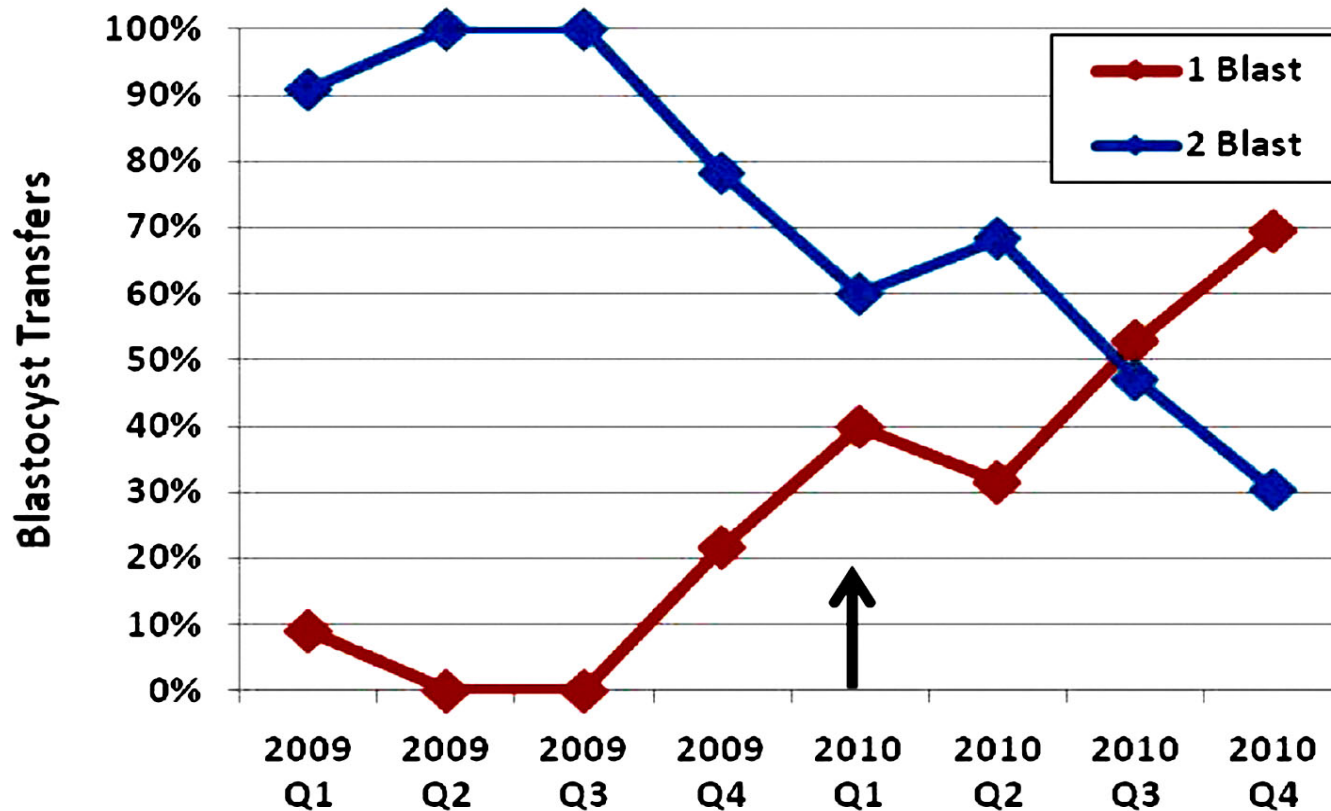


Single Embryo Transfer

Edited by
Jan Gerris, G. David Adamson,
Petra De Sutter and
Catherine Racowsky

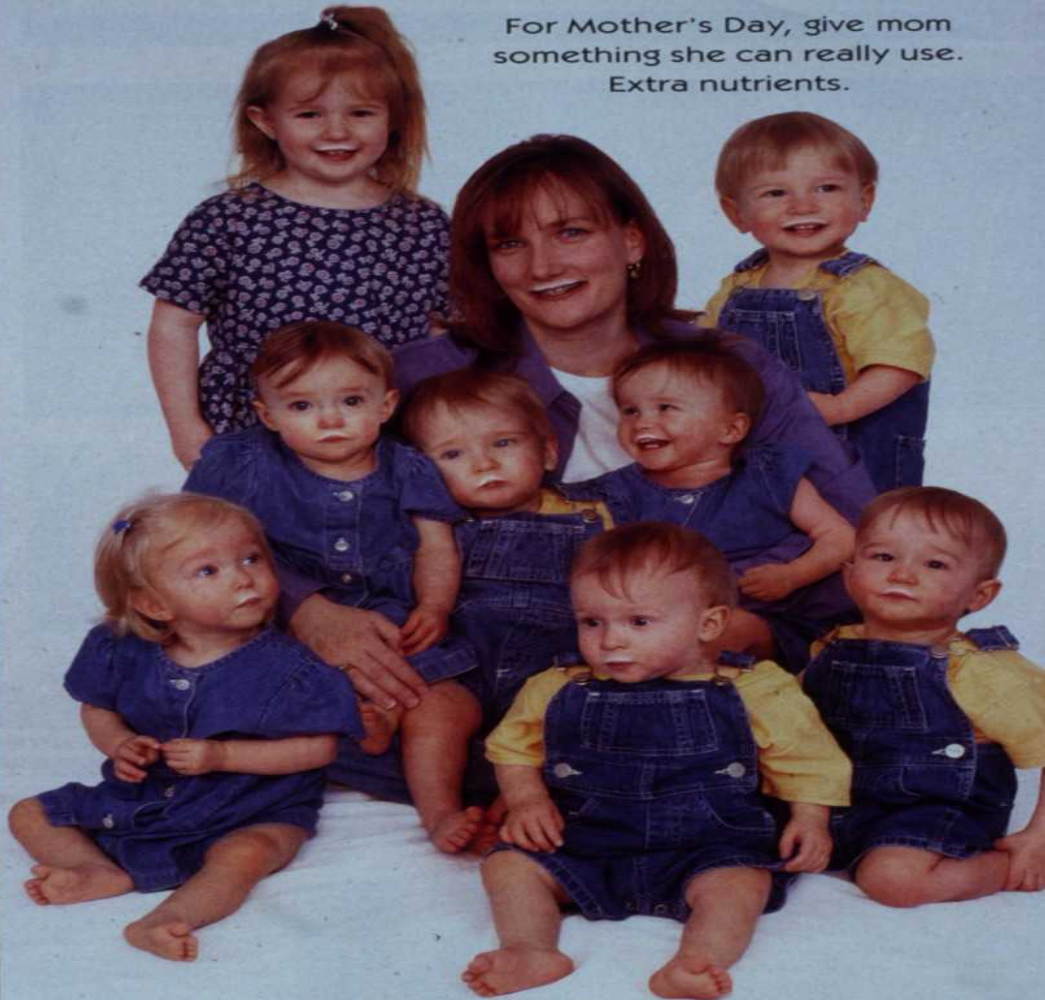
CAMBRIDGE
Medicine

Summary of the percentage of blastocysts transferred per patient (y axis) over time per quarter year (Q1–4) from 2009 to 2010 (x axis). Transfers of a single blastocyst (*red line*) increased after the institution of the mandatory single-blastocyst transfer (mSBT) policy as marked with an arrow in January 2010. Conversely, the percentage of two blastocyst transfers (*blue line*) decreased after the mSBT policy. No patient had more than two blastocysts transferred, so the total percentage of embryos transferred each quarter equals 100%.



Csokmay JM, Hill MJ, Chason RJ, Hennessy S, James AN, Cohen J, DeCherney AH, Segars JH, and Payson MD. Experience with a patient-friendly, mandatory, single-blastocyst transfer policy: the power of one. *Fertility and Sterility*® Vol. 96, No. 3, September 2011.

For Mother's Day, give mom
something she can really use.
Extra nutrients.



got milk?

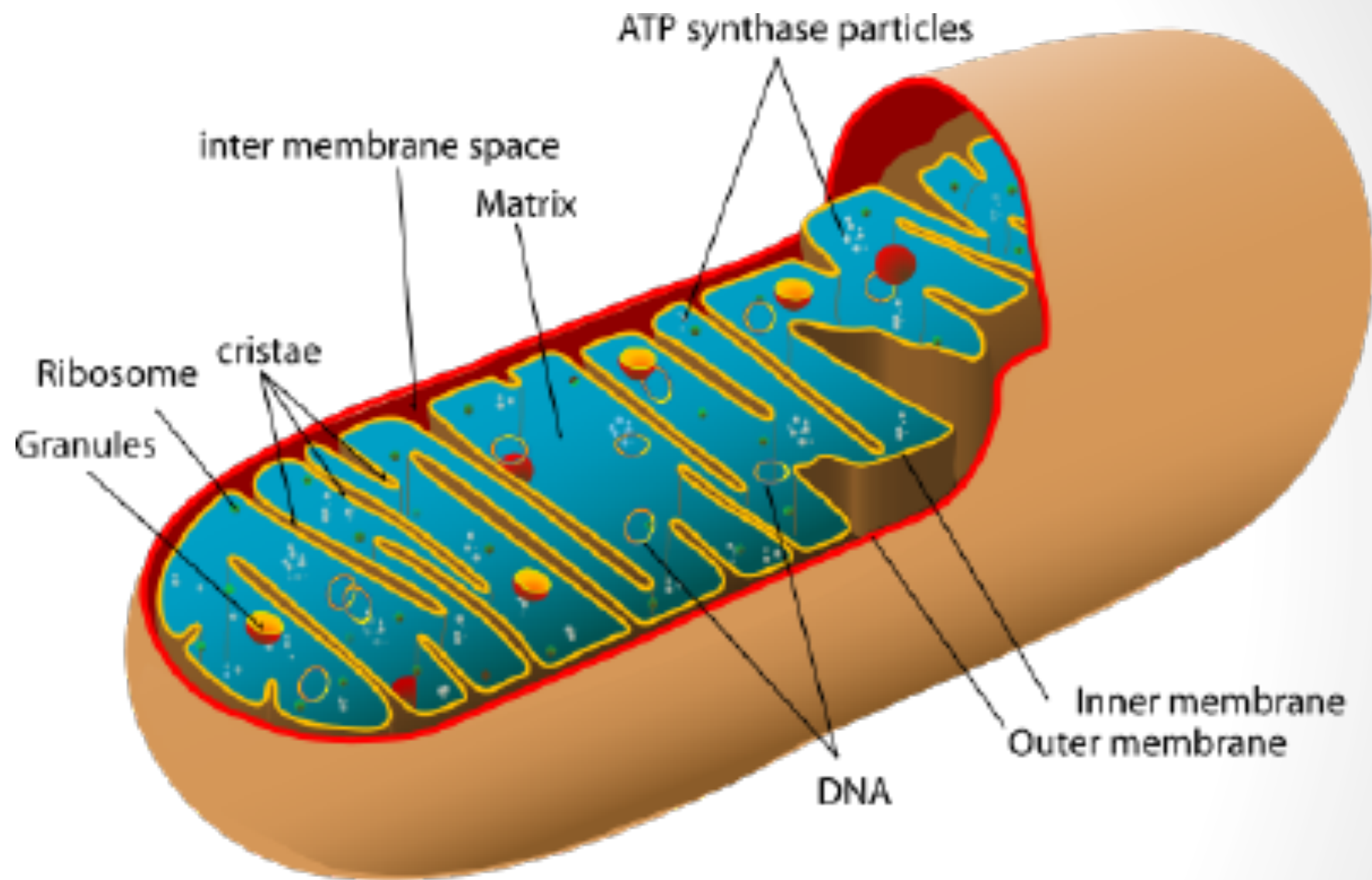
MILKAUGHTS © 1999 NATIONAL FLUID MILK PROCESSOR PROMOTION BOARD

THE LAW

- Embryo ownership
- Surrogacy
- Embryo research
- Cloning
- regulation

Ethics

- Sex selection
- Post mortem reproduction
- Frozen embryo storage
- Disease perpetuation
- Single women





*"For his fifth birthday, I've got tickets to 'The Lion King.'
So, ideally, I'd like to conceive by the end of this month."*